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Assessment of environmental tobacco smoke exposure in children with asthmatic symptoms by questionnaire and cotinine concentrations in plasma, saliva, and urine

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Abstract

To validate a detailed questionnaire for assessment of environmental tobacco smoke (ETS) exposure by the biomarker cotinine in various media, a population-based study in the urban area of Malmö, Sweden was performed in children aged 8–13 years with and without asthmatic symptoms. There were strong correlations between urinary and saliva cotinine concentrations and also, though to a lesser extent, between these media and plasma. Even a detailed questionnaire gave only a rough picture of the ETS exposure, as indicated by the biomarkers. In a multivariate model, the most significant questionnaire-derived predictor of the cotinine levels was the maternal smoking habits; other questionnaire variables gave only a minimal explained variance. Children with a history of asthmatic symptoms had statistically significantly *lower* median cotinine levels in urine and saliva compared to referent children, most likely because of the antismoking information to their parents. This should be considered in epidemiological studies of ETS risks.

Keywords: Asthma; Change in smoking prevalence; Cotinine environmental tobacco smoke; Questionnaire

1. Introduction

Increased prevalence of maternal smoking as well as levels of the nicotine metabolite cotinine in urine was found in consecutive new cases of severe childhood asthma, compared to referent children, indicating that ETS exposure is a risk factor [1]. However, the relationship between ETS exposure and asthma in different studies has not been consistent [2]. This could be due to different study designs. For example, we know little about the smoking behavior of parents of children with asthma after the onset of symptoms.

Further, the exposure assessment in most investigations are based on self-reports [3]; hence, they could be biased [4]. For example, there is a possibility of deceptive underreporting of exposure in children by smoking parents. Further, several factors are of importance for the exposure, such as the amount of tobacco smoked, room size, ventilation, and proximity to smokers. Also, exposure may occur outside the home, for example, in cars [5]. It may be difficult to estimate these factors in a questionnaire. Biomarkers of ETS exposure may be used for validation of ETS questionnaire.

We found that cotinine, determined in saliva [6] and in urine [7], were useful as biomarkers of ETS exposure. Plasma levels have also been used [8]. However, the relationship between concentrations of cotinine in plasma, saliva, and urine and ETS exposure has not been investigated.

Therefore, in the present study, the relationships between information on ETS exposure in a detailed ETS questionnaire, on the one hand, and cotinine concentrations in plasma, saliva, and urine on the other were investigated in children who suffered asthma and in referents.

2. Material and methods

2.1. Subjects

Out of a population sample of urban children ($N = 2684$) living in southern part of Sweden [9], who had answered a questionnaire on airways symptoms and exposures, all 137

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children with asthmatic symptoms living in Malmö, Sweden were, during the winter (November–January), invited to a medical examination, including sampling of plasma, saliva, and urine. However, 52 children [mean age: 10.3 (8–13) years, 31 (60%) were boys] did not participate for different reasons, including acute illness. There was some information about smoking in the initial questionnaire ("Do anyone smoke indoors at home?"); this information indicates that, among asthmatic children, ETS exposure may have been higher among the nonparticipating children (25/52; 48%) than the participants (30%). In addition, 27 children (1 drop-out) who reported no asthmatic symptoms in the questionnaire, and who were matched for sex, age, and living area with the asthmatic ones, were examined. Thus, a total of 111 children participated. Their mean age was 11 years (range 8–13), 63 (46%) were boys, 105 provided urine samples, 102 saliva, and 78 plasma for the determination of cotinine. All children and their parents had given their written consent before participating in the study. The study was approved by the Ethics Committee of Lund University.

2.2. Questionnaire

The questionnaire contained issues on respiratory symptoms (previous or current attacks of wheezing, dyspnoea, dry cough, asthma diagnosed by a physician, or asthma treatment) and was answered by the parents and their children. It contained 16 questions (Table 2) about ETS exposure. Hence, the parents were asked whether they smoked, the current number of cigarettes/pipes per day, whether they smoked indoors at home, how much they had smoked in the last 3 days prior to the study, and whether friends or others smoked in the children's homes. The parents were also asked for how long they had smoked (cigarette pack-years = years of smoking × daily consumption in grams/20), including one question whether anyone smoked (at least 6 months) during the first 2 years of their child's life. The educational level of both parents was determined by the number of years in education. Also, the living space (in m^2) was asked about. There were missing questionnaire data on maternal ($N = 1$) or paternal smoking ($N = 3$) because the children were of divorced parents.

2.3. Medical examination

All participating children were examined by a physician verifying the diagnosis of asthma. In addition, all participants performed a lung function test determining the bronchial responsiveness to methacholine. The area under the dose–response curve (AUC) expressed as arbitrary units was median 15 times smaller (i.e., indicating bronchial responsiveness) in the asthmatic children as compared to the healthy controls (unpublished data).

2.4. Plasma and saliva cotinine

Plasma and saliva cotinine was determined by a capillary gas–liquid chromatographic method using nitrogen phosphorus detection [10]. An aqueous solution of 5-methylcotinine was used as an internal standard. The analytical range was 0.1–1000 μg/l using a 100-μl sample. The average coefficient of variation over the cotinine analytical range of 1–1000 μg/l was 2.1%.

2.5. Urinary cotinine

A gas chromatography mass spectrometry (GC-MS) [5] method using positive ion chemical ionization with ammonia reagent was employed for the measurement of urinary cotinine. The ions monitored were the $m/z = 177$ and $m/z = 180$, corresponding to the $(M+H)^+$ ions of cotinine and the trideuterated cotinine used as the internal standard. The detection limit was 0.1 μg/l. The quantitative assay typically involved six calibration standards, the lowest standard being 0.2 ng/ml. The relative standard deviations were less than 5% ($n = 30$) at all calibration levels with a correlation coefficient of $r = 0.998$. Absolute area reproducibility for the highest calibration standard for 24 individual calibration curves was 5.8% (relative standard deviation). Two aliquots from each sample were prepared and two GC-MS determinations were made on each sample.

2.6. Urinary creatinine

Creatinine (crea) was measured in each urine sample by use of KODAK EKTACHEM Clinical Chemistry Slides and a Kodak Ektachem 700 XR-C Analyzer (Department of Clinical Chemistry, University Hospital, Lund).

2.7. Statistics

Undetectable cotinine concentrations were set at 0.05 μg/l. Because the cotinine concentrations were skew, nonparametric models, or logarithmic transformation, were used. Mann-Whitney *U*-test was used for evaluation of group differences and Spearmans' rank (r_s) to assess correlations. In a few cases, linear regression lines are given.

All exposure variables from the questionnaire were analyzed univariately, using linear regression. Backwards stepwise regression was performed with level of probability to remove of 0.10. Possible interactions have been carefully considered but were found not to be relevant. The SPSS package for Windows® was used for all calculations.

3. Results

3.1. Cotinine and questionnaire data on ETS exposure

The median levels of cotinine in children were low (plasma 0.60 μg/l; saliva 0.30 μg/l; urine 0.53 μg/g crea) in homes who reported no indoor smoking, and increased considerably with smoking in the home by parents or others (Table 1). If both parents (with or without other smokers) reported that they were currently smoking in their home, the median cotinine concentrations in children were about 3, 9, and 17 times higher for plasma, saliva, and urine, respectively, compared to homes with no indoor smoking.

Most important for the cotinine level in a child was the maternal smoking habit (Table 1). The cotinine levels in

Table 1
Relationship between the concentrations of the environmental tobacco smoke biomarker cotinine in plasma, saliva, and urine in children and questionnaire data on parental smoking habits (yes/no)

	Cotinine concentrations								
	Plasma			Saliva			Urine		
Who smokes indoors at home?	N	Median (μg/l)	Range (μg/l)	N	Median (μg/l)	Range (μg/l)	N	Median (μg/g crea)	Range (μg/g crea)
None	51	0.60	0.20–1.9	63	0.30	0.10–1.4	65	0.53	<0.10–6.0
None of the parents, but others	2	1.3	0.60–1.9	2	1.2	0.50–1.8	2	4.3	1.2–7.3
Father only, but not mother ± others	3	0.90	0.80–1.8	2	1.5	1.0–1.9	3	4.5	2.1–7.9
Mother only, but not father ± others	9	1.9*	0.70–2.4	15	1.6*	0.50–4.2	16	6.3*	1.9–24
Both parents ± others	9	1.4*	0.60–4.0	16	2.6*	0.60–5.4	15	8.9*	1.1–45
Total	74	0.79	0.20–4.0	98	0.62	0.10–5.4	101	1.7	<0.10–45

*P < 0.001, compared to the none smoking group.

plasma (r_s = 0.59, P < 0.0001), saliva (Fig. 1a) and urine (Fig. 1b) of her child were significantly correlated with the number of cigarettes generally smoked by her at home.

The paternal smoking was also associated with cotinine levels in their children; however, the correlations (number of cigarettes smoked: r_s = 0.40; r_s = 0.53; r_s = 0.41 with plasma, saliva, and urinary cotinine levels, respectively; all Ps < 0.01) were weaker than for maternal smoking.

Consequently, there was a highly significant association between the cotinine levels in children and the total reported amount of tobacco smoked indoors by parents and others. However, the correlations for plasma (r_s = 0.59, N = 72; P < 0.0001), saliva (Fig. 2a) and urine (Fig. 2b), all were only marginally better than for maternal smoking. However, the cotinine levels varied considerably between children of parents with the same reported smoking habits. The educational level of both the mother (P = 0.006) and father (P < 0.03) were statistically significantly inversely correlated with the urinary cotinine levels (Table 2). Also, the educational level of the mother was significantly inversely associated with her smoking intensity (P = 0.01).

Information on smoking habits was available in two different formats (current smoking, i.e. number of cigarettes per day, and lifetime smoking, i.e. pack-years and smoking during infancy). However, due to the short half time of cotinine (about 18 h) and the strong correlation between the current and life-time smoking (r_s = 0.78, 0.58 and 0.50 for maternal, paternal and other, respectively) only the analyses based on current smoking are presented. In the backwards stepwise regression model, all variables that were believed to have a relation with cotinine levels, based on a theoretical concept, were entered (Table 2). All variables but maternal and paternal smoking were removed, leaving a final model that explained 34.6% of the variance in cotinine levels.

3.2. Relationship between plasma, saliva and urinary cotinine concentrations

There were close associations between plasma, saliva, and urinary cotinine concentrations. The best correlation was found between urinary and saliva cotinine (r_s = 0.86, P < 0.0001). The correlation between plasma cotinine, on the one hand, and

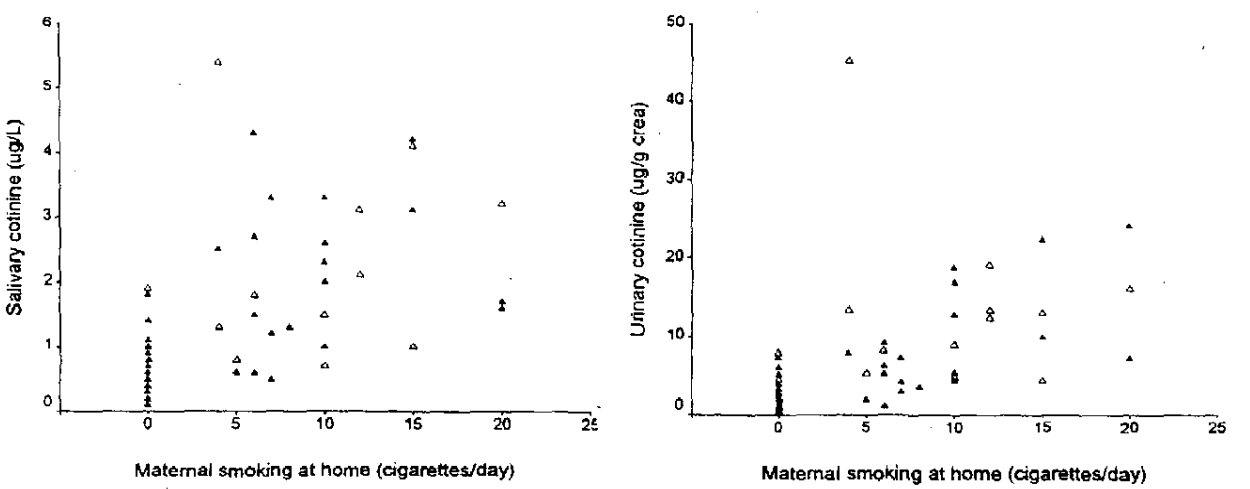

Fig. 1. (a) Relationship between salivary cotinine concentrations in 101 children (78 asthmatic, closed symbols; 23 controls, open) and questionnaire data on the intensity of maternal smoking at home (r_s = 0.70, P < 0.0001). (b) Relationship between urinary cotinine concentrations in 104 children (83 asthmatic, closed symbols; 21 controls, open) and questionnaire data on the intensity of maternal smoking at home (r_s = 0.74, P < 0.0001).

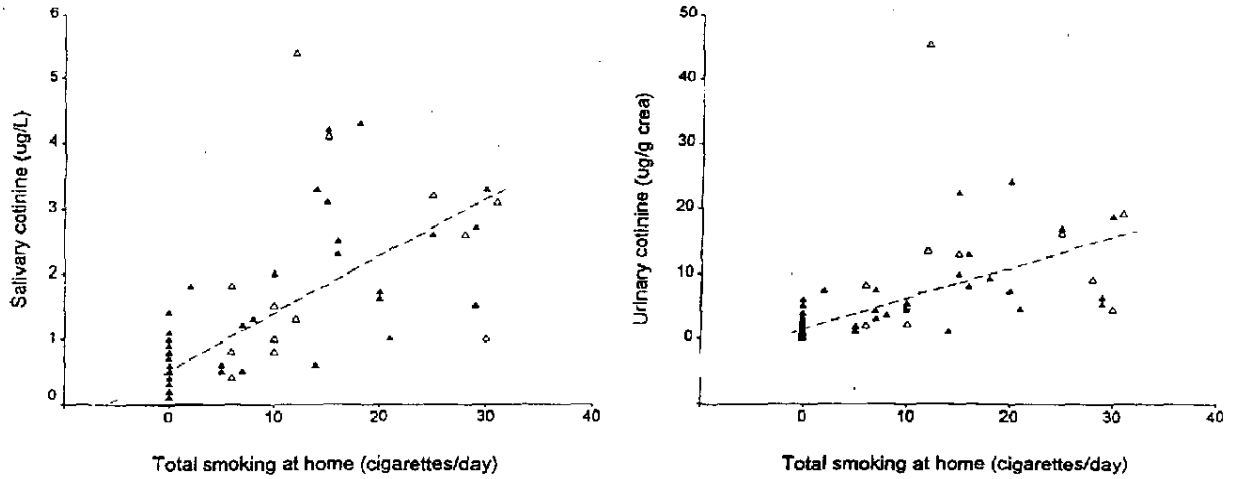

Fig. 2. (a) Relationship between salivary cotinine concentrations in 96 children (77 asthmatic, closed symbols; 19 controls, open) and questionnaire data on the total intensity of indoor smoking at home ($r_s = 0.74$, $P < 0.0001$). (b) Relationship between urinary cotinine concentrations in 98 children (82 asthmatic, closed symbols; 16 controls, open) and questionnaire data on the total intensity of indoor smoking at home ($r_s = 0.76$, $P < 0.0001$).

saliva ($r_s = 0.71$, $P < 0.0001$) and urinary ($r_s = 0.69$, $P < 0.0001$) cotinine, on the other, were somewhat lower.

3.3. ETS exposure in children with and without asthma

According to the questionnaire data, *at the time of the study*, the smoking prevalence in homes of children with a history of "asthma" was only 30% vs. 73% in homes of the referents. An obvious change in the parental smoking pattern of asthmatic children had taken place since the infancy of their children. The prevalence of anyone smoking at home during the children's *first 2 years of life* was 50% in children with asthma and 77% in the controls. Thus, 43% of parents of children with asthmatic symptoms had quit smoking compared to only 5% of the parents of healthy children ($P = 0.04$).

The average total number of cigarettes smoked indoors was significantly *lower* in homes of children with a history of asthmatic symptoms than in the referent children (means 4.1 vs. 10.1 cigarettes per day; $P = 0.002$).

The cotinine levels in children with a history of "asthma" were much lower than in the referents (Table 3).

There was no statistically significant difference in cotinine levels between children with previous and current symptoms, nor were there any associations with the severity of symptoms.

There was no significant different in cotinine levels in children with asthmatic symptoms, who had had contact with the health care system (physicians diagnosis or medication; medians: plasma: 1.1 μg/l; saliva: 0.35 μg/l; urine: 1.2 μg/g crea; $N = 13$), compared to those without ($N = 72$; plasma 0.6 μg/l; saliva: 0.50 μg/l; urine 1.0 μg/g crea).

4. Discussion

The most interesting findings of the present study were: a detailed questionnaire on ETS exposure only explained a limited fraction of the variance in the biomarkers of ETS exposure; maternal smoking was most important; plasma, saliva, and urinary cotinine concentrations in children were closely associated, but with a variation; and children with a history of asthmatic symptoms had lower current ETS exposure than referent children, in spite of the fact that the latter were few.

Selection biases could be a problem in studies of passive smoking. Indeed, the response rate was lower in the children with a history of asthma compared to the referents. However, this was mostly due to an ongoing influenza epidemic. Asthmatic children may be more sensitive; associations between ETS exposure and respiratory infections (and

Table 2
Questionnaire variables as potential predictors of log urinary cotinine in children in the univariate analyses

Independent variable	Adjusted R^2	P-value
Age	−0.009	0.81[a]
Gender	0.000	0.32[a]
Smoking during infancy	0.31	<0.001
Living space	−0.009	0.76[a]
Maternal education	0.062	0.006[a]
Paternal education	0.043	0.026[a]
Smoking last 3 days	0.12	<0.001[a]
Cigarettes/day mother	0.305	<0.001[a]
Cigarettes/day father	0.15	<0.001[a]
Cigarettes/day other	0.098	0.001[a]
Pack-years indoors mother	0.24	<0.001
Pack-years indoors father	0.17	<0.001
Pack-years indoors other	0.022	0.078
Pack-years outdoors mother	0.078	0.003
Pack-years outdoors father	0.083	0.003
Pack-years outdoors other	0.010	0.16

[a]Included in the multivariate regression model.

Table 3
Concentrations of the environmental tobacco smoke biomarker cotinine in plasma, saliva, and urine in children with current and previous asthmatic symtoms (grouped according to severity) and in controls (healthy)

		Cotinine concentrations								
		Plasma (μg/l)			Saliva (μg/l)			Urine (μg/g crea)		
Time	Symptom	N	Median (μg/l)	Range	N	Median (μg/l)	Range	N	Median (μg/g crea)	Range
Currently	Dry cough	14	1.2	0.40–4.0	14	0.90	0.10–4.3	18	2.2*	<0.10–19
	Wheezing	6	0.50	0.40–2.1	10	0.60*	0.10–1.7	10	0.60**	<0.10–7.2
	Wheezing and dyspnoea	18	0.80	0.20–2.4	28	0.50*	0.10–4.2	29	1.6**	<0.10–22
Previously	Physician's diagnosis/medication	12	1.3	0.20–2.4	13	1.0	0.10–3.3	13	0.60*	<0.10–17
but not now	Symptoms only	11	0.60**	0.40–1.8	13	0.30***	0.10–1.6	13	0.70**	<0.10–24
Currently or	Total	61	0.70****	0.20–4.0	78	0.50**	0.10–4.3	83	1.3***	<0.10–24
previously	No (controls)	17	1.1	0.30–2.4	24	1.2	0.10–5.4	22	6.6	<0.10–45

Compared to the control group: *$P < 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$; ****$P = 0.08$.

asthma) have been reported by several authors [2]. Thus, there is a possibility that some children with ETS-associated asthma may not have joined the study. Indeed, the initial questionnaire indicated a higher prevalence of ETS exposure among the nonparticipating children. This may have caused some underestimate of the ETS exposure in children with a history of asthmatic symptoms. However, this cannot explain but a fraction of the difference between the children with and without asthma. Further, the possible selection bias should not have any impact on the main aims of the study: relationship between cotinine concentrations and questionnaire data on ETS exposure, and associations between cotinine concentrations in the different biological matrices.

The levels of cotinine in saliva and urine were similar to those we have found earlier in children [1,11–14]. Relatively few ETS studies have used plasma determinations; however, the present levels agree with those in adult nonsmokers [8]. Further, the present study confirmed findings by us [1,11,12,14] and others [15,16] of a general association between cotinine in saliva and urine, on the one hand, and parental smoking habits, on the other, and that maternal smoking is the most significant predictor of the child's cotinine levels. The very low median levels in children with no one smoking at home showed that parental smoking is the main cause of ETS exposure in children.

However, there was a variation in cotinine concentrations at a certain level of parental smoking. In theory, this could be explained by analytical imprecision; however, our methods are much more precise than this variation. Further, uptake, metabolism and excretion of cotinine could vary among individuals. However, in human experimental studies, we did not find any large interindividual differences in concentrations or kinetics [7]; preschool children, though younger than the present ones, had higher urinary cotinine concentrations than older ones, probably due to a higher relative ETS dose. Of course, the variation may, in part, be due to misclassification of smoking status. Such is assumed to be rather unusual for "no" or "yes" [11,17], but may be considerable as regards quantification. The multivariate model based on detailed questionnaire data on ETS exposure could only explain 35% of the variance in urinary cotinine levels. Indeed, a detailed questionnaire gave no better information than just a few questions. This shows that several factors (e.g., proximity to smokers, room size, ventilation, and exposure outside home) that can affect ETS exposure are difficult to determine using a questionnaire. Hence, the objective biomarkers are valuable, especially in older children and adults, as the potential for ETS exposure in different environments is even more varied for them, compared to very young children.

Some authors (e.g., [18]) have claimed that some foods contain nicotine, and that this could distort the findings when using cotinine as a marker of ETS exposure. However, there are no human data to support it. Pirkle *et al.* [19] demonstrated that the number of people required to detect a contribution from dietary sources is so large that logistically it would be impossible to perform such a study. Our investigations of nonsmoking subjects avoiding ETS exposure showed extremely low levels of cotinine in urine [7]. Moreover, the levels increased 100-fold with experimental ETS exposure [5,7].

The association between cotinine in children and the educational level of their parents is in agreement with other reports [12,13,20]. In the present study, it could be explained by a higher intensity of smoking by parents with lower educational level. This is in agreement with a higher prevalence of smoking in low socioeconomic strata [21]. An additional explanation could be that the educational level is associated with social class, which, in turn, is related to the size of the home (i.e., a larger house would dilute the interior ETS) [20]. However, in this study there was no statistically significant association between living space and cotinine levels.

The validity of cotinine determination has been questioned, because of a claimed large interlaboratory variation [22]. In this study, there were fairly good associations between the levels in the three different biological matrices. The correlation between urinary cotinine determined by

GC-MS and saliva cotinine determined by GC with nitrogen phosphorous detection was particularly good. This demonstrates good precision. Other studies have also shown a good correlation between cotinine levels in plasma and saliva [23,24], but in this particular study the plasma levels were difficult to measure due to interferences in the chromatograms. The source of the interference is unknown.

Thus, cotinine is a good marker of recent ETS exposure. Interestingly, also past smoking habits and cigarette pack-years were associated with present cotinine levels in the child. This shows that during the children's life nicotine exposure (i.e., parental smoking) is rather stable. Similarly, Jarvis *et al.* [25] found stable saliva cotinine levels in a follow-up study of adolescents. To some extent, there may be an exposure from nicotine in house dust [26], which may stay for a long time, even after smoking has stopped in the home. Willers *et al.* [7] have shown that such exposure to nicotine is possible. In the present study, however, there was a significant decrease in smoking at home. Thus, the low cotinine levels in the present children with asthma does not indicate that nicotine in house dust is an important source for exposure.

This study showed lower ETS exposure, as indicated by both questionnaires and cotinine levels, in children with mainly slight asthmatic symptoms than in referent children. The present findings contrast to the higher levels found in an earlier study of children, who had newly developed severe asthmatic symptoms. The different types of asthma cases could explain the discrepancy. Questionnaire data indicated a change in the parental smoking pattern of the asthmatic children, probably to reduce the ETS exposure. This is in agreement with findings of Forsberg *et al.* [9], who, in a much larger cohort that included the present children, showed an association between asthma and ETS exposure during the first years of life; later these parents avoided exposing their children to tobacco smoke. This finding should be important when designing epidemiological studies on passive smoking risks.

Interestingly, there was a relatively low parental smoking prevalence during infancy in the "asthma" group; this may be explained by the antismoking information during pregnancy to parents of susceptible children.

ETS exposure in the children with asthmatic symptoms, who earlier had been in contact with the health care system, was at the same level as those who had not. This indicates that the reduction of parental smoking may not be an effect on the antismoking information by the health care system only, but rather the general antismoking information given in society, especially by the media.

On the other hand, the effect may be selective to children with airways symptoms. Thus, the cotinine levels in the referent children were found to be similar to what we found in a population sampled 8 years earlier (medians 6.6 vs. 4.81 μg/l) [11]. This is supported by tobacco sales statistics, which showed no decrease in the amount of tobacco sold ([27]; Swedish tobacco company, unpublished data).

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References

[1] Willers S, Svenonius E, Skarping G. Passive smoking and childhood asthma—urinary cotinine levels in children with asthma and referents. Allergy 1991;46:330–4.

[2] Halken S, Höst A, Nilsson L, Taudorf E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. Allergy 1995;50:97–105.

[3] Kawachi I, Colditz GA. Confounding, measurement error, publication bias in studies of passive smoking. Am J Epidemiol 1996;144:909–15.

[4] Lee PN. "Marriage to a smoker" may not be valid marker of exposure in studies relating environmental tobacco smoke to risk of lung cancer in Japanese non-smoking women. Int Arch Occup Environ Health 1995;67:287–94.

[5] Skarping G, Willers S, Dalene M. Determination of cotinine in urine using glass capillary gaschromatography and selective detection, with special reference to the biological monitoring of passive smoking. J Chromatogr 1988;454:293–301.

[6] Jarvis MJ. Application of biochemical intake markers to passive smoking measurement and risk estimation. Mutat Res 1989;222:101–10.

[7] Willers S, Skarping G, Dalene M, Skerfving S. Urinary cotinine in children and adults during and after semi-experimental exposure to environmental tobacco smoke. Arch Environ Health 1995;50:130–8.

[8] Kemmeren JM, Poppel G, Jarvis MJ. Plasma cotinine: stability in smokers and validation of self-reported smoke exposure in non-smokers. Environ Res 1994;66:235–43.

[9] Forsberg B, Pekkanen J, Clench-Aas J, Mårtensson MB, Stjernberg N, Bartonova A, Timonen K, Skerfving S. Childhood asthma in four regions in Scandinavia: risk factors and avoidance effects. Int J Epidemiol 1997;26:610–19.

[10] Feyerabend C, Russell MAH. A rapid gas–liquid chromatographic method for the determination of cotinine and nicotine in biological fluids. J Pharm Pharmacol 1990;42:450–2.

[11] Willers S, Attewell R, Bensryd I, Schütz A, Skarping G, Vahter M. Exposure to environmental tobacco smoke in the household and urinary cotinine excretion, heavy metals retention, and lung function. Arch Environ Health 1992;47:357–63.

[12] Jarvis MJ, Phil M, Strachan DP, Feyerabend C. Determinants of passive smoking in children in Edinburgh, Scotland. Am J Publ Health 1992;82:1225–9.

[13] Cook DG, Whincup PH, Jarvis MJ, Strachan DP, Papacosta O, Bryant A. Passive exposure to tobacco smoke in children aged 5–7 years: individual, family, and community factors. BMJ 1994;308:384–9.

[14] Jarvis MJ, Russell MAH, Feyerabend C, Eiser JR, Morgan M, Gammage P, Gray EM. Passive exposure to tobacco smoke: saliva cotinine concentrations in a representative population sample of non-smoking schoolchildren. Br Med J 1985;291:927–9.

[15] Dell'Orco V, Forastiere F, Agabiti N, Corbo G, Pistelli R, Pacifici R, Zuccaro P, Pizzabiocca A, Rosa M, Altieri I, Perucci C. Household and community determinants of exposure to involuntary smoking: a study of cotinine in children and adolescents. Am J Epidemiol 1995;142:419–27.

[16] Bono R, Russo R, Arossa W, Scursatone E, Gilli G. Involuntary exposure to tobacco smoke in adolescents: urinary cotinine and environmental factors. Arch Environ Health 1996;51:127–131.

[17] Pokorski TL, Chen WW, Bertholf RL. Use of urine cotinine to validate smoking self-reports in US Navy recruits. Addict Behav 1994; 19:451–4.

[18] Domino EF. Estimating exposure to environmental tobacco smoke [Letter to the Editor]. JAMA 1996;276:603.

[19] Pirkle JL, Bernert JT, Etzel RA, Flegal KM, Brody DJ, Maurer KR. Estimating exposure to environmental tobacco smoke [Reply to the Editor]. JAMA 1996;276–604.

[20] Henschen M, Frischer T, Pracht T, Spiekerkötter E, Karmaus W, Meinert R, Lehnert W, Wehrle E Kuehr J. The internal dose of passive smoking at home depends on the size of the dwelling. Environ Res 1997;72:65–71.

[21] National Swedish Department of Health and Social Welfare. Tobacco habits in Sweden (in Swedish). ISBN 91-38-09131-3. 1986.

[22] Biber A, Scherer G, Hoepfner I, Adlkofer F, Heller W-D, Haddow JE, Knight GJ. Determination of nicotine and cotinine in human serum and urine: an interlaboratory study. Toxicol Lett 1987;35:45–52.

[23] Jarvis MJ, Russell MAH, Benowitz NL, Feyerabend C. Elimination of cotinine from body fluids: implications for noninvasive measurement of tobacco smoke exposure. Am J Public Health 1988;78:696–8.

[24] Curvall M, Elwin DE, Kazemi-Vala E, Warholm C, Enzell CR. The pharmacokinetics of cotinine in plasma and saliva from non-smoking healthy volunteers. Eur J Clin Pharmacol 1990;38:281–7.

[25] Jarvis MJ, McNeill AD, Russell MA, West RJ, Bryant A, Feyerabend C. Passive smoking in adolescents: one-year stability of exposure in the home. Lancet 1987;1(8545):1324–5.

[26] Willers S, Hein HO, Schütz A, Suadicani P, Gyntelberg F. Cadmium and lead levels in house dust from smokers' and non-smokers' homes related to nicotine levels. Indoor Environ 1993;2:14–8.

[27] Statistics, Sweden. Statistical Yearbook of Sweden 1994. Official Statistics of Sweden. Published by Statistics Sweden. ISBN 91-618-0611-0/ISSN 0081-5381. Norstedts Tryckeri AB, Stockholm 1993; 80:117.